PB88-179460

Health Effects Assessment for Beryllium and Compounds

(U.S.) Environmental Protection Agency
Cincinnati, OH

Jul 87

U.S. Department of Commerce
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1. REPORT NO.	2.	3. RECIPIENT'S ACCESSION NO.
EPA/600/8-88/020		PB88 179460/AS

4. TITLE AND SUBTITLE	5. REPORT DATE
Health Effects Assessment for Beryllium and Compounds	July 1987
	6. PERFORMING ORGANIZATION CODE
7. AUTHOR(S)	8. PERFORMING ORGANIZATION REPORT NO.
9. PERFORMING ORGANIZATION NAME AND ADDRESS	10. PROGRAM ELEMENT NO.
	11. CONTRACT/GRANT NO.
12. SPONSORING AGENCY NAME AND ADDRESS Environmental Criteria and Assessment Office Office of Research and Development U.S. Environmental Protection Agency Cincinnati, OH 45268	13. TYPE OF REPORT AND PERIOD COVERED
	14. SPONSORING AGENCY CODE EPA/600/22

15. SUPPLEMENTARY NOTES

16. ABSTRACT

This report summarizes and evaluates information relevant to a preliminary interim assessment of adverse health effects associated with specific chemicals or compounds. The Office of Emergency and Remedial Response (Superfund) uses these documents in preparing cost-benefit analyses under Executive Order 12991 for decision-making under CERCLA. All estimates of acceptable intakes and carcinogenic potency presented in this document should be considered as preliminary and reflect limited resources allocated to this project. The intent in these assessments is to suggest acceptable exposure levels whenever sufficient data are available. The interim values presented reflect the relative degree of hazard associated with exposure or risk to the chemical(s) addressed. Whenever possible, two categories of values have been estimated for systemic toxicants (toxicants for which cancer is not the endpoint of concern). The first, RfD_S or subchronic reference dose, is an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs during a limited time interval. The RfD is an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs for a significant portion of the lifespan. For compounds for which there is sufficient evidence of carcinogenicity, q_1^*s have been computed, if appropriate, based on oral and inhalation data if available.

17. KEY WORDS AND DOCUMENT ANALYSIS

a. DESCRIPTORS	b. IDENTIFIERS/OPEN ENDED TERMS	c. COSATI Field/Group

18. DISTRIBUTION STATEMENT	19. SECURITY CLASS *(This Report)*	21. NO. OF PAGES
Public	Unclassified	69
	20. SECURITY CLASS *(This page)*	22. PRICE
	Unclassified	A04 $4.95 / 6.95 MF

PB88-179460

EPA/600/8-88/020
July, 1987

HEALTH EFFECTS ASSESSMENT FOR BERYLLIUM AND COMPOUNDS

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REPRODUCED BY
U.S. DEPARTMENT OF COMMERCE
NATIONAL TECHNICAL
INFORMATION SERVICE
SPRINGFIELD, VA. 22161

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PREFACE

This report presents a brief summary and evaluation of information relevant to a preliminary interim assessment of adverse health effects associated with beryllium and compounds. All estimates of acceptable intakes and carcinogenic potency presented in this document should be considered as preliminary reflecting limited resources allocated to this project. Pertinent toxicologic and environmental data were located through on-line literature searches of the Chemical Abstracts, TOXLINE and the CHEMFATE/DATALOG data bases. The basic literature searched supporting this document is current up to May, 1986. Secondary sources of information have also been relied upon in the preparation of this report and represent large scale health assessment efforts that entail extensive peer and Agency review. The following Office of Health and Environmental Assessment (OHEA) sources have been extensively utilized:

U.S. EPA. 1980a. Ambient Water Quality Criteria Document for Beryllium. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Water Regulations and Standards, Washington, DC. EPA 440/5-80-024. NTIS PB81-117350.

U.S. EPA. 1986a. Health Assessment Document for Beryllium. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH. EPA 600/8-84/026B.

U.S. EPA. 1986b. Drinking Water Criteria Document for Beryllium. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Drinking Water, Washington, DC.

U.S. EPA. 1986c. Integrated Risk Information System (IRIS). Reference Dose (RfD) for Oral Exposure for Beryllium. Online (verification date 12/02/85). Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH.

The intent in these assessments is to suggest acceptable exposure levels for noncarcinogens and risk cancer potency estimates for carcinogens whenever sufficient data were available. Values were not derived or larger uncertainty factors were employed when the variable data were limited in scope tending to generate conservative (i.e., protective) estimates. Nevertheless, the interim values presented reflect the relative degree of hazard or risk associated with exposure to the chemical(s) addressed.

Whenever possible, two categories of values have been estimated for systemic toxicants (toxicants for which cancer is not the endpoint of concern). The first, RfD_S (formerly AIS) or subchronic reference dose, is an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs during a limited time interval (i.e., for an interval that does not constitute a significant portion of the lifespan).

This type of exposure estimate has not been extensively used, or rigorously defined, as previous risk assessment efforts have been primarily directed towards exposures from toxicants in ambient air or water where lifetime exposure is assumed. Animal data used for RfD_S estimates generally include exposures with durations of 30-90 days. Subchronic human data are rarely available. Reported exposures are usually from chronic occupational exposure situations or from reports of acute accidental exposure. These values are developed for both inhalation (RfD_{SI}) and oral (RfD_{SO}) exposures.

The RfD (formerly AIC) is similar in concept and addresses chronic exposure. It is an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs for a significant portion of the lifespan [see U.S. EPA (1980b) for a discussion of this concept]. The RfD is route-specific and estimates acceptable exposure for either oral (RfD_O) or inhalation (RfD_I) with the implicit assumption that exposure by other routes is insignificant.

Composite scores (CSs) for noncarcinogens have also been calculated where data permitted. These values are used for identifying reportable quantities and the methodology for their development is explained in U.S. EPA (1984).

For compounds for which there is sufficient evidence of carcinogenicity RfD_S and RfD values are not derived. For a discussion of risk assessment methodology for carcinogens refer to U.S. EPA (1980b). Since cancer is a process that is not characterized by a threshold, <u>any</u> exposure contributes an increment of risk. For carcinogens, q_1^*s have been computed, if appropriate, based on oral and inhalation data if available.

ABSTRACT

In order to place the risk assessment evaluation in proper context, refer to the preface of this document. The preface outlines limitations applicable to all documents of this series as well as the appropriate interpretation and use of the quantitative estimates presented.

Beryllium has been shown to be carcinogenic in experimental animals following inhalation exposure. Epidemiology studies of beryllium workers are inadequate to demonstate or refute that beryllium is a carcinogen. Using the U.S. EPA (1986d) weight of evidence ranking system, beryllium has been judged to be a Group B2 carcinogen, i.e., a probable human carcinogen as supported by a sufficient level of animal data. U.S. EPA (1986a) calculated inhalation risk estimates from studies in which animals were exposed to beryllium compounds with higher solubilities, although these estimates have not been finalized nor is there a recommendation as yet as to the best characterization of the inhalation cancer risk. Risk estimate values are given in the Appendix.

The U.S. EPA (1986b) has recommended an oral q_1^* of 4.88 $(mg/kg/day)^{-1}$ for beryllium based on the evidence presented in the Schroeder and Mitchener (1975a) study.

ACKNOWLEDGEMENTS

The initial draft of this report was prepared by Syracuse Research Corporation under Contract No. 68-03-3112 for EPA's Environmental Criteria and Assessment Office, Cincinnati, OH. Dr. Christopher DeRosa and Karen Blackburn were the Technical Project Monitors and John Helms (Office of Toxic Substances) was the Project Officer. The final documents in this series were prepared for the Office of Emergency and Remedial Response, Washington, DC.

Scientists from the following U.S. EPA offices provided review comments for this document series:

Environmental Criteria and Assessment Office, Cincinnati, OH
Carcinogen Assessment Group
Office of Air Quality Planning and Standards
Office of Solid Waste
Office of Toxic Substances
Office of Drinking Water

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LIST OF ABBREVIATIONS

BCF	Bioconcentration factor
BCR	Beryllium Case Registry
CAS	Chemical Abstract Service
CHO	Chinese hamster ovary
CS	Composite score
DNA	Deoxyribonucleic acid
DWEL	Drinking water exposure level
HA	Health advisory
NOAEL	No-observed-adverse-effect level
ppm	Parts per million
RfD	Reference dose
RfD_I	Inhalation reference dose
RfD_O	Oral reference dose
RfD_S	Subchronic reference dose
RfD_{SI}	Subchronic inhalation reference dose
RfD_{SO}	Subchronic oral reference dose
RNA	Ribonucleic acid
TLV	Threshold limit value
TWA	Time-weighted average

1. ENVIRONMENTAL CHEMISTRY AND FATE

Beryllium is a metallic element that belongs to Group IIA of the periodic table and has an oxidation state of +2. Average crustal rock contains ~2.8 µg beryllium/g; beryllium also occurs in more concentrated forms as a component of >40 minerals (U.S. EPA, 1986a). Average estimates of abundance in earth's crust ranges from 2-10 ppm.

Beryllium occurs in environmental samples at concentrations of ~0.01-0.1 ng/m³ in air, 0.05-0.1 µg/g in house dust, 0.01-1.0 ng/g in surface water, 0.3-6.0 µg/g in soil and 0.01 µg/g in biological materials. Some plants, such as hickory, may accumulate as much as 1 µg/g dry weight beryllium (U.S. EPA, 1986a). Physical properties of beryllium and some of its compounds are listed in Table 1-1.

Since most atmospheric beryllium is derived from coal combustion, it is likely that its chemical form would be beryllium oxide. Conversion to ionized salts is possible, but it has not been reported. Removal of beryllium from the atmosphere takes place by wet and dry deposition. It is reported that most beryllium found in stack emissions is found on particles <1 µm; particles of this size remain aloft for ~10 days. Assuming that half of the beryllium emitted into the atmosphere returns to earth as wet precipitation, the average concentration of beryllium in rain or snow is expected to be 0.01 ng/g (U.S. EPA, 1986a).

Beryllium from the atmosphere eventually reaches the soil and sediment where it is probably retained in the relatively insoluble form of beryllium oxide (U.S. EPA, 1986a). Beryllium is strongly fixed in many soils and will displace divalent cations that share common sorption sites in soils (Fishbein, 1981).

TABLE 1-1

Physical Properties of Beryllium and Some of Its Compounds*

Compound	CAS Number	Molecular Formula	Atomic or Molecular Weight	Form	Melting Point (°C)	Boiling Point (°C)	Water Solubility
Beryllium	7440-41-7	Be	9.01	gray metallic, hexagonal	1278±5	2500	insoluble
Beryllium chloride	7787-47-5	$BeCl_2$	79.92	colorless needles, deliquescent	405	520 (488)	43.52 g/100 g (30°C)
Beryllium fluoride	7787-49-7	BeF_2	47.01	colorless, amorphous	sublimes 800	NR	18 g/ℓ (25°C)
Beryllium nitrate	7787-55-5	$Be(NO_2)_2 \cdot 3H_2O$	187.07	white-yellow crystalline, deliquescent	60	142	very soluble
Beryllium oxide	1304-56-9	BeO	25.01	white, hexagonal	2530±30	~3900	0.20 mg/ℓ (30°C)
Beryllium sulfate	7787-56-6	$BeSO_4$	105.07	NA	decomposes 550-600	NR	29.3 g/100 g (25°C)

*Source: Weast, 1983

NR = Not relevant; NA = not available

Sufficient data could not be located in the available literature to evaluate the fate and persistence of beryllium in water and soil. Since oxides and hydroxides of beryllium are relatively insoluble at the common pH of natural water, most beryllium will be present in the sediments. The residence time of beryllium in the ocean has been estimated to be about a few hundred years (Fishbein, 1981). An estimated weighted average BCF of 19 for beryllium in the edible portion of fish and shellfish suggests that beryllium will not bioaccumulate significantly in aquatic organisms (U.S. EPA, 1980a).

2. ABSORPTION FACTORS IN HUMANS AND EXPERIMENTAL ANIMALS

2.1. ORAL

Data regarding the efficiency of gastrointestinal absorption of beryllium are equivocal. In a study by Crowley et al. (1949), rats were given a single oral dose of ^{7}Be solution by stomach tube and were sacrificed 8 days later. The ^{7}Be content of the tissues and excreta was determined. Following this protocol, the absorption of ^{7}Be could not be demonstrated, although the authors reported that if any absorption took place, it was <0.2%.

Furchner et al. (1973) gave single oral doses of carrier-free ^{7}Be to mice, rats, monkeys and beagle dogs. The mice and rats were anesthetized and dosed by oral intubation; dogs received a gelatin capsule containing the dose; and monkeys received sugar cubes with the appropriate dose. A second experiment was also conducted in which rats ingested 10 mL of a saccharin-glucose solution containing ^{7}Be for 56 days. Results of both experiments showed little absorption. Absorption from a single dose was estimated to be ~0.6% with a urinary:fecal ratio of 0.0011, while the average urinary:fecal ratio during the 56 days of exposure was 0.0044. Hyslop et al. (1943) also indicated that <1% of ingested beryllium is absorbed.

Reeves (1965) studied the absorption of beryllium in rats provided with drinking water containing beryllium sulfate. The average daily beryllium intake was ~6.6 or 66.6 µg, and the rats were treated for up to 24 weeks. Beryllium intake was measured and recovery in several organs and tissues, urine and feces was determined. The results showed that 60-90% of the ingested beryllium was eliminated in the feces, indicating higher levels of absorption than studies previously reviewed. Total recovery of beryllium, however, ranged from 60-91% (average, 79.3%) of estimated intake values.

Reeves (1965) concluded that because of the low solubility of beryllium in intestinal fluid, the compound was precipitated as the phosphate and was not available for absorption. The author also surmised that most of the beryllium found in the body was absorbed from the stomach where pH (3.0-3.6 in the rat) is favorable for maintaining beryllium salts in their ionized and soluble form. If beryllium is absorbed predominantly from the stomach, it is reasonable to postulate that absorption would be dependent on gastric emptying time, which can be highly variable, thus leading to a range of beryllium absorption efficiencies.

2.2. INHALATION

Animal studies indicate that beryllium is retained and absorbed by the lungs. In a study described by Reeves et al. (1967) and Reeves and Vorwald (1967), rats were exposed to beryllium sulfate at an average beryllium concentration of 35 μg/m³, 7 hours/day, 5 days/week for 72 weeks. Lung beryllium concentrations reached a plateau of ~13.5 μg (in whole lungs) after 36 weeks of exposure. At the same time, a plateau in the beryllium concentration of the tracheobronchial lymph nodes was also reached.

In a study by Zorn et al. (1977), rats and guinea pigs were exposed to beryllium sulfate aerosol with ^{7}Be added as the chloride. Animals were exposed for 3 hours and were sacrificed either immediately after the exposure period or 20-408 hours postexposure. The total amount of beryllium inhaled was <3 mg (of which, 10 ng was ^{7}Be). Immediately following exposure, ~5 ng of ^{7}Be was retained, 67% in the lungs and 15% in the skeleton.

Hart et al. (1984) exposed rats for 1 hour to beryllium oxide fired at 560°C. The average beryllium concentration was 477 μg/m³, and 90% of the particles had a mean diameter of ≤1 μm. At sacrifice, the lungs of rats were lavaged and both the lung tissue and lavage fluid were analyzed

for beryllium. At 2.5 hours after exposure, ~200 ng of beryllium was found in the lung tissue. This amount remained constant in rats sacrificed throughout the 3-week postexposure period. The amount of beryllium found in the lavage fluid decreased from 280 to 16 ng during the 3-week study period. Hart and Pittman (1980) demonstrated the ability of macrophages to take up particles of insoluble beryllium compounds. U.S. EPA (1986a) implied that inhaled beryllium on contact with respiratory epithelium may form insoluble phosphates that are taken up by macrophages.

3. TOXICITY IN HUMANS AND EXPERIMENTAL ANIMALS

3.1. SUBCHRONIC

3.1.1. Oral. Pertinent data regarding the toxicity of beryllium following subchronic oral exposure could not be located in the available literature.

3.1.2. Inhalation. Two types of disease resulting from inhalation exposure to beryllium compounds have been described in humans (Constantinidis, 1978). The first type, acute berylliosis, is more likely to occur shortly after a massive exposure to beryllium compounds or may occur after a prolonged exposure to lower concentrations of beryllium compounds. The second form, chronic berylliosis, is highly variable in onset, varying with the length of exposure and time from last exposure. The chronic disease can develop $\geq$20 years after the last exposure. Because of the longer period of time usually required to develop the chronic disease, it will be discussed in Section 3.2.2.

Acute berylliosis can affect any level of the respiratory tract, causing rhinitis, pharyngitis, tracheobronchitis, and may lead to severe pulmonary involvement depending on the exposure (Constantinidis, 1978). Inflammation extending into the lower respiratory tract tends to occur after intense exposure. Acute pneumonitis can also occur after beryllium exposure. The symptoms of this syndrome include shortness of breath, malaise, anorexia, weight loss, coughing, cyanosis, tachypnea and tachycardia. The majority of acute cases of beryllium disease resolve completely within a few months but fatal cases are not unusual (Dutra, 1948). It has been estimated that chronic disease may develop in ~6% of patients with acute berylliosis (Hardy, 1965).

In the United States, the first case of acute berylliosis was reported in 1943 by Van Ordstrand et al. (1943). In the 1940s, hundreds of cases occurred, but with improvements in working conditions lowering beryllium exposure the number of cases has greatly decreased (U.S. EPA, 1986a). The U.S. BCR, a file on reported cases of acute and chronic beryllium disease, started in 1952, lists 215 cases of acute disease up to 1967 (Freiman and Hardy, 1970) and 9 additional cases from 1967-1983 (Eisenbud and Lisson, 1983).

Several animal studies of the subchronic inhalation toxicity of beryllium have been conducted, and these were reviewed by Vorwald et al. (1966).

In one study, rats were exposed to beryllium sulfate aerosol at concentrations ranging from 2.8-194 $\mu g/m^3$, 7 hours/day for 1-560 days. It was stated that exposure to 2.8 $\mu g/m^3$ did not produce any specific inflammatory abnormalities, while exposures to 21 $\mu g/m^3$ resulted in significant inflammatory changes in some longer lived rats. At 42 $\mu g/m^3$, chronic pneumonitis was noted, while exposure to 194 $\mu g/m^3$ resulted in acute berylliosis. An increased incidence of pulmonary cancer was also noted.

In a study by Schepers et al. (1957), 115 male and female Sherman and Wistar rats were exposed to beryllium sulfate at an average beryllium concentration of 12γ/ft^3 or 35 $\mu g/m^3$, 8 hours/day, 5 days/week and 4 hours/day, 1 day/week for 180 days. A group of 139 rats was maintained as controls. During the exposure period, 46 beryllium-exposed rats died from (primarily) pleural pericarditis with a tendency to chronic pneumonitis. No bacteria were isolated, but the authors concluded that the response was caused by an infection because sulfathiazole treatment had a beneficial effect. At the end of the 6-month exposure period, 17 rats were sacrificed.

The majority of these rats had pulmonary effects including foam-cell clusters, infiltration of macrophages, lobular septal-cell proliferation, and periobronchial and alveolar-wall epithelialization. One rat exhibited focal metaplasia of alveolar walls, another had granulomas in the lungs, while a third rat and possibly several others had adenomas. None of these lesions were observed in groups of three to four control rats/strain sacrificed every 2 months. The surviving rats (52) were then maintained in beryllium-free air for up to 18 months. In these rats, a progressive increase in the frequency of pulmonary changes was observed. Histological examination of the lungs of these rats revealed emphysema of the atropic vesicular type and metaplasia of the bronchial epithelium in an unspecified number of rats. Pulmonary tumors were also observed (Section 4.2.2).

3.2. CHRONIC

3.2.1. Oral. A number of chronic oral studies of beryllium toxicity are available. In several early studies (Guyatt et al., 1933; Jacobson, 1933; Kay and Skill, 1934), rickets was produced in young animals by administering large doses of beryllium carbonate (0.1-0.5%, 1000-5000 mg/kg food). This effect has since been regarded as an indirect result of the binding of phosphate to beryllium in the gut and, consequently, phosphorus depletion in the body.

The chronic oral toxicity of beryllium in rats (Schroeder and Mitchener, 1975a) and mice (Schroeder and Mitchener, 1975b) at a low dose was studied. Groups of 52 male and 52 female Long-Evans rats and 54 male and 54 female Swiss mice were provided with drinking water containing beryllium sulfate at 5 ppm from the sulfate for their lifetimes. Similar groups of rats and mice were maintained as controls. At various intervals throughout the studies,

body weights of rats and mice were recorded. At the time of natural death, rats and mice were dissected and any gross pathological changes were noted. Blood and urine samples were also taken from rats.

The results in rats showed a slight depression in growth of male rats from the ages of 2-6 months, and no effect on the lifespan of treated rats compared with controls. Glucose levels in urine of female rats were higher than controls ($p<0.025$, Chi-square analysis), but no other differences were found in analyses of urine, serum glucose and cholesterol or fasting uric acid levels when compared with controls (Schroeder and Mitchener, 1975a). In mice, no consistent difference between treated and control animals was noted (Schroeder and Mitchener, 1975b).

U.S. EPA (1980a, 1986a) reviewed a 2-year feeding study by Morgareidge et al. (1977), in which rats were fed dietary concentrations of 5, 50 and 5000 ppm beryllium from the sulfate. The 5000 ppm dose level resulted in a slight decrease in body weight. Carcinogenic effects observed in this study are discussed in Section 4.2.1.

3.2.2. Inhalation. In humans, inhalation exposure to beryllium can result in chronic berylliosis. Since this disease is probably a result of hypersensitization to beryllium, the length of exposure may not be critical. The disease may occur $\geq$20 years or more after beryllium exposure has ended, and stress conditions (e.g., pregnancy) can produce a flare-up of the disease (Tepper et al., 1961).

Although fluorescent lamp manufacturing is no longer a beryllium exposure problem, chronic berylliosis was first reported by Hardy and Tabershaw (1946), who presented data on 17 cases in individuals employed in the fluorescent lamp manufacturing industry. In most patients, the symptoms first appeared months or even years after exposure. The majority of patients were women and most were younger than 30. Lung x-rays indicated a

progression from fine granularity to a diffuse reticular pattern to distinct nodules in the third stage of the disease. In <2 years of illness, 5/17 patients died. Disability persisted in most cases, although some recovery was noted in two cases. Postmortem examination of the lungs of one patient showed a granulomatous inflammation.

In addition to abnormalities in lung X-rays, other signs and symptoms of the chronic disease include fatigue, chest pain, cyanosis, clubbing of the fingers, hepatomegaly, splenomegaly, cardiac failure, renal stones and pneumothorax (Hall et al., 1959). Other findings were hypercalcemia, hypercalcuria and osteosclerosis (Stoeckle et al., 1969), as well as hyperuricemia (Kelley et al., 1969).

Hall et al. (1959) presented data on 601 cases listed in the BCR. The chronic disease accounted for 61% of the cases, although 28 cases were classified as both acute and chronic. In men, 227/418 were acute cases, while in women, only 2 cases were acute. The chronic disease was more likely to be fatal; 31% of the chronic disease patients died compared with 6% of the acute cases. A long latency period was indicated; in >20% of the cases recorded in the BCR before 1959, the time since last exposure was >5 years with a maximum of 15 years.

A more recent report (Eisenbud and Lisson, 1983) provides data on 622 cases of the chronic disease. Among the cases examined, 577 were occupationally-exposed to beryllium, 42 were attributed to ambient air exposure (areas around plants) and 23 to dust exposure in the home. The authors reported that up to 40 years may elapse between initial exposure and onset of disease, so that more recently exposed individuals may still develop the disease.

Infante et al. (1980) conducted a mortality study on 421 living white males listed in the BCR during the period of 1952 through 1975 with a diagnosis of beryllium-related nonneoplastic respiratory symptoms or disease. During this period, 139 subjects died from all causes, compared with 65.89 expected deaths, based on cause-specific mortality rates for the general white male population of the United States. The excess of ~73 deaths observed in this study was predominantly the result of non-neoplastic respiratory disease (52 deaths) other than influenza and pneumonia (1.6 expected). Of the total 139 deaths, heart disease was responsible for 31 compared with 29.9 expected, 19 were due to cancer (12.41 expected) and the cause of death was unknown in 15 subjects. Remaining deaths (22 subjects) were due to all other causes.

Evidence that beryllium exposure may result in excess deaths from heart disease or respiratory disease is provided by a mortality study by Wagoner et al. (1980). This study involved a cohort of 3055 white male workers exposed to beryllium for varying lengths of time from 1942-1967 at the Kawecki-Berylco Industries site in Pennsylvania. During the period of investigation, 875 deaths occurred compared with 817 expected. Significant increases in deaths from heart disease [396 observed vs. 349 expected ($p<0.05$)] and respiratory disease, other than influenza and pneumonia [31 observed vs. 18.7 expected ($p<0.01$)], were noted. The expected numbers of cases were based on mortality rates of 1965-1967 for the white male population of the United States.

A number of investigators have studied respiratory function of beryllium-exposed workers (Andrews et al., 1969; Kanarek et al., 1973; Sprince et al., 1978, 1979; Cotes et al., 1983; Preuss and Oster, 1980). These studies do not clearly indicate that measurements of respiratory function parameters

are related to beryllium exposure. Cotes et al. (1983) concluded that respiratory function studies generally could not detect beryllium disease before radiographic changes appeared, while Preuss and Oster (1980) noted that changes in vital capacity may occur long before X-ray changes appear.

Evidence that chronic beryllium disease has an immunological component has been provided by a number of investigators. Curtis (1951) developed a patch test that was positive for most cases of dermatitis and skin granuloma, and positive for many cases of lung disease caused by beryllium (Nishimura, 1966). The patch test, however, could also initiate the development of skin reactions or pulmonary disease in people exposed to beryllium, but who had not shown previous symptoms of respiratory illness (Sneddon, 1955; Stoeckle et al., 1969; Rees, 1979; Cotes et al., 1983).

Williams and Williams (1983) found that the lymphocyte transformation test gave a positive response in 16 patients with established chronic beryllium disease, while it was negative in 10 subjects with suspected disease. Only two positive responses were reported among 117 healthy beryllium workers. Similar results were also reported by Van Ordstrand (1984). It is not clear if a positive test in a healthy worker indicates that the individual is at a higher risk for developing pulmonary disease.

In an area in Czechoslovakia, where coal with a high beryllium content is burned, Bencko et al. (1980) found that plant workers and people living in the vicinity of the plant had higher levels of IgG and IgA and autoantibodies compared with an unexposed control group. Since many factors may contribute to higher immunoglobin levels, the significance of these findings is not clear.

Beryllium sensitivity has been observed in some strains of guinea pigs but not others (Chiappino et al., 1969; Reeves et al., 1971, 1972; Barna et

al., 1981). Because these studies were of relatively short duration and include exposure by intratracheal injection, they will not be discussed further.

Reeves et al. (1967) exposed groups of 75 male and 75 female Sprague-Dawley rats to beryllium sulfate at a mean concentration of beryllium of 34 μg/m³, 7 hours/day, 5 days/week for up to 72 weeks. Control of the exposure concentration was poor (the standard deviation of the mean level was 24 μg/m³). Similar groups of rats were maintained as controls. Every month, three male and three female rats from the exposed and control groups were sacrificed. Among the findings were progressive increases in lung weight in the exposed rats; at the end of the experiment, the lung weights of exposed rats were on an average of >4 times those of controls. Histological examination of the lungs showed inflammatory and proliferative changes. Clusters of macrophages in the alveolar spaces were also a common finding. Granulomatosis and fibrosis were only occasionally seen. The proliferative changes ultimately led to the generation of tumors in all the exposed rats (43/43), sacrificed or dead at ≥13 months.

3.3. TERATOGENICITY AND OTHER REPRODUCTIVE EFFECTS

Pertinent data regarding teratogenic and other reproductive effects of beryllium following oral or inhalation exposure were not located in the available literature.

3.4. TOXICANT INTERACTIONS

Synergistic effects of beryllium have been noted. Uzawa (1963) found that beryllium oxide potentiated the carcinogenic effect of 20-methylcholanthrene to a greater degree than did carbon black. Stokinger et al. (1950) reported a synergistic effect of fluoride ion; beryllium fluoride produced nearly a doubling of the acute toxic effect of beryllium sulfate when inhaled at any given concentration.

4. CARCINOGENICITY

4.1. HUMAN DATA

4.1.1. Oral. Berg and Burbank (1972) studied the relationship between trace metal concentrations in drinking water and cancer deaths in 15 regions of the United States, 10 of which included entire states that were relatively well-sampled. In the analysis, both frequency of detection and the average detected concentration of the metal were considered. Correlations between beryllium concentration and cancer death rate were significantly positive for cancers of the breast, bone and uterus, with probability of positive association ranging from 0.006-0.040. Mortality rates for regions with beryllium in the water were excessive only for nonwhite males. The highest mean level of beryllium was 0.3 µg/ℓ found in Delaware, Maryland, West Virginia and Kentucky. The results of this study are based on imperfect analytical methods and sampling, and the positive associations for beryllium in drinking water and cancer are not proof of cause and effect relationships (U.S. EPA, 1986b).

4.1.2. Inhalation. Infante et al. (1980) studied lung cancer mortality by the retrospective cohort method in white males listed in the BCR. The study cohort included 421 members of the BCR, <50% of the total. Of these, vital status could not be determined on 64 (15%), while 139 (33%) were found to have died by December 31, 1975. In the 139 members that died, the cause of death could not be ascertained for 15 individuals.

The results of this study showed that in terms of total cancer, 19 deaths were observed vs. 12.41 expected, based on cancer specific mortality rates for white males in the U.S. population. With respect to lung cancer, 6 deaths occurred >15 years after the onset of beryllium exposure vs. 2.81 expected ($p<0.01$). These expected lung cancer deaths were calculated from a

NIOSH life table program, which has been shown to result in an 11% excess in the calculated expected number of lung cancer deaths (Wagoner et al., 1980). Adjusting the number of expected deaths, the Infante et al. (1980) p value is reduced to one of borderline significance (6 observed vs. 3.21 expected; $p<0.09$).

Infante et al. (1980) also divided the cohort on the basis of "acute" vs. "chronic" beryllium disease. Subjects were considered acute if the BCR records indicated a diagnosis of chemical bronchitis or pneumonitis or other acute respiratory illness at time of entry into the registry. Subjects were called chronic if BCR records indicated a diagnosis of pulmonary fibrosis or some recognized chronic lung condition at time of entry into the registry. The remaining cases, which could not be designated as chronic, were considered by Infante et al. (1980) to be acute if the onset of the disease occurred within 1 year of initial exposure. These designations are not the medically accepted definitions of acute and chronic beryllium disease; cases of beryllium disease lasting $\leq$1 year are acute, while those lasting >1 year are chronic (U.S. EPA, 1986a). The authors found no significant excess in lung cancer in their chronic respiratory disease group of 198 persons (1 observed death vs. 1.38 expected); however, in their acute respiratory disease group of 223 subjects, they observed 6 lung cancer deaths vs. 1.91 expected ($p<0.05$) and, in the interval of >15 years since initial onset of beryllium exposure, 5 observed cancer deaths vs. 1.56 expected ($p<0.05$). The expected deaths used for these comparisons were also determined using the NIOSH life tables, so the results must be regarded as questionable.

A number of studies of lung cancer in beryllium exposed workers from two plants have been conducted (Bayliss et al., 1971; Bayliss and Lainhart, 1972; Bayliss and Wagoner, 1977; Wagoner et al., 1980; Mancuso and El-Attar,

1969; Mancuso, 1970, 1979, 1980). These studies have been described in detail in U.S. EPA (1986a,b) and are summarized in Table 4-1.

In an evaluation of the total database regarding the relationship of lung cancer with occupational exposure to beryllium, the U.S. EPA (1986a) noted several limitations. None of these studies are independent since all are studies of basically the same group of workers. Extensive cooperation existed between the authors of all these studies; they all used the NIOSH life table program known to produce an 11% underestimate of expected lung cancer deaths at the time. Furthermore, the authors could not adequately address the confounding effects of smoking or of exposure to other potential carcinogens received during prior and subsequent employment in other non-beryllium industries in the area known to produce potential carcinogens (especially in beryllium workers with short-term employment). Problems in design and execution of the studies (e.g., incomplete delineation of the cohort) further weaken the findings. There appeared to be a tendency for the authors to overemphasize the positive nature of their results and minimize the contribution of qualifying factors. If the problems in these studies were addressed, the finding of a significant excess risk would probably no longer be apparent, although the possibility remains that a portion of the remaining excess lung cancer risk may be partially due to beryllium exposure. Thus, U.S. EPA (1986a,b) concluded that despite the problems with the epidemiology studies, they must be considered to be at least suggestive of a carcinogenic risk in humans.

4.2. BIOASSAYS

4.2.1. Oral. Chronic oral studies of beryllium have not resulted in statis- tically significant increases in tumors in treated animals compared with controls. Schroeder and Mitchener (1975a,b) provided mice and rats

TABLE 4-1

Comparison of Study Cohorts and Subcohorts of Two Beryllium Companies*

Company Where Employed	Source	Period of Employment	Comparison Population	Termination Date of Follow-up	Chief Lung Cancer Results	Reference
KBI, BRUSH 6818 males	personnel records	1942-1967	U.S. males	1967	total: 36 (O), 34.1 (E)	Bayliss et al., 1971
KBI only 3795 white males	same as above	1942-1967	U.S. white males	1967	total: 25 (O), 23 (E) latency 15 years+: 14(O), 13.3 (E)	Bayliss and Lainhart, 1972
KBI-Reading facility only 3070 white males	same as above	1942-1967	U.S. white males	1975	total: 46 (O), 33 (E) ($p<0.05$) latency 15 years+: 37 (O), 24(E) ($p<0.05$)	Bayliss and Wagoner, 1977
KBI-Reading facility only 3055 white males	same as above	1942-1967	U.S. white males	1975	total: 47 (O), 34.3 (E) latency 15 years+: 20 (O), 10.8 (E) ($p<0.05$)	Wagoner et al., 1980
KBI, BRUSH 3685 white males	social security quarterly earnings reports	1937-1948	industrial control (unidentified)	1966	equivocal	Mancuso and El-Attar, 1969
KBI, BRUSH 3685 white males	social security quarterly earnings reports	1937-1944 and 1945-1948	internal control	1966	duration of employment (rate): ≥1.25 years, 33.2/10^5 <1.25 years, 99.9/10^5 prior respiratory disease only: with 284.3/10^5 without 77.7/10^5	Mancuso, 1970
KBI-2044 BRUSH-1222 white males	same as above	1942-1948	U.S. white males	Brush 1974 KBI	latency 15 years+ only: Ohio - 22 (O), 9.9 (E) ($p<0.01$) Pennsylvania - 36 (O), 22 (E) ($p<0.01$) mobility (deaths): among departments, 80 (O), 57.1 (E) ($p<0.01$)	Mancuso, 1979
KBI 3685 white males	same as above	1937-1948	viscose rayon workers	1976	remained in same department: 80 (O), 50.6 (E) ($p<0.01$)	Mancuso, 1980

*Source: U.S. EPA, 1986a,b

KBI = Kawecki-Berylco Industries (Pennsylvania); BRUSH = Brush Beryllium Company (Ohio); (O) = observed; (E) = expected

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with drinking water containing beryllium sulfate at 5 ppm beryllium. They reported a slight increase in leukemias in female mice (9/52 treated, 3/47 control) (Schroeder and Mitchener, 1975b), and a slightly higher incidence of grossly observed tumors in male rats (9/33 treated, 4/26 control) (Schroeder and Mitchener, 1975a). These increases were not statistically significant in either species.

In a study by Morgareidge et al. (1975), groups of 50 Wistar rats were provided with diets containing beryllium sulfate at 0, 5, 50 or 500 ppm beryllium for 104 weeks. The highest survival rate and the least number of pathological lesions (of all treated groups) were found in the highest dose group. Reticulum cell sarcoma in the lung was seen in all dose groups and in controls, and the same lesions were seen in lymph nodes, bone marrow and unspecified abdominal organs. The incidence of lung reticulum cell sarcoma was higher in males than females and was statistically significant in males at the two lower doses but not at the high dose. Although the authors stated that "there was probably no statistical difference in reticulum-cell sarcoma between the observed incidence in the different groups" and that "there is no dose-incidence relationship, with the highest incidence occurring in the low-level group," their tabular data show statistical significance. In an analysis of this study, U.S. EPA (1986b) determined that the incidence of lung reticulum cell carcinoma in males was significant by the Fisher exact test in the two lowest groups (5 ppm,, p=0.0065; 50 ppm, p=0.036). This study is considered to be suggestive of a carcinogenic response to ingested beryllium, but the lack of a response at the high dose and the fact that the study was not published or (presumably) peer-reviewed, severely limits interpretation as a positive study (U.S. EPA, 1986b).

4.2.2. Inhalation. Numerous animal studies have indicated that inhalation exposure to beryllium and beryllium-containing substances may result in pulmonary tumors. These studies are briefly presented in Table 4-2. Schepers et al. (1957) noted eight histologically distinct types of tumors in the lungs of exposed rats. Intrathoracic metastases were commonly observed and transplantations were frequently successful.

In the series of experiments by Vorwald (1953, 1962), the incidence of lung tumors in exposed rats appeared to be weakly positively correlated with exposure concentration and duration. Reeves and Deitch (1969), on the other hand, stated that tumor yield in rats depended on age at exposure rather than on duration of exposure. These investigators determined that exposure for only 3 months at an early age gave a tumorigenic response similar to exposure for 18 months. Reduced tumor counts were observed in rats exposed for 3 months later in life. In all cases, a latency period of ~9 months from initiation of exposure seemed to be required.

Of 20 female rhesus monkeys intermittently exposed to beryllium phosphate, beryllium sulfate or beryllium fluoride for 8 months, lung tumors were observed in only one (Schepers, 1964). Intermittent exposure of rhesus monkeys for $\geq$36 months to beryllium sulfate, however, was associated with development of lung tumors in 8/11 (Vorwald, 1968).

4.3. OTHER RELEVANT DATA

In addition to being a carcinogen in laboratory animals following inhalation exposure, beryllium has also been shown to be carcinogenic following intratracheal and intravenous injections, and implantation into bone. Several studies (Vorwald and Reeves, 1959; Spencer et al., 1968, 1972; Ishinishi et al., 1980; Groth et al., 1972, 1976, 1980; Groth and McKay, 1971) involved intratracheal administration of beryllium and compounds into rats and one study (Vorwald et al., 1966) involved rhesus monkeys.

TABLE 4-2

Pulmonary Carcinoma from Inhalation Exposure of Animals to Beryllium[a]

Compound	Species	Atmospheric Concentration (mg/m³ as Be)	Weekly Exposure Time (hours)	Duration of Exposure (months)	Incidence of Pulmonary Carcinoma	Reference
Beryllium sulfate	rats	33-35	33-38	12-14	4/8 (females)	Vorwald, 1953
		33-35	33-38	13-18	17/17	Vorwald et al., 1955
		32-35	44	6-9, followed by 18-month observation period	58/136	Schepers et al., 1957
		55	33-38	3-18	55/74	Vorwald, 1962
		180	33-38	12	11/27	Vorwald, 1962
		18	33-38	3-22	72/103	Vorwald, 1962
		18	33-38	8-21	31/63	Vorwald, 1962
		18	33-38	9-24	47/90	Vorwald, 1962
		18	33-38	11-16	9/21	Vorwald, 1962
		1.8-2.0	33-38	8-21	25/50	Vorwald, 1962
		1.8-2.0	33-38	9-24	43/95	Vorwald, 1962
		1.8-2.0	33-38	13-16	3/15	Vorwald, 1962
		21-42	33-38	18	almost all	Vorwald et al., 1966
		2.8	33-38	18	13/21	Vorwald et al., 1966
		34	35	13	43/43 (females)	Reeves et al., 1967
		36	35	3	19/22 (both sexes)	Reeves and Deitch, 1969
		36	35	6	33/33 (both sexes)	Reeves and Deitch, 1969
		36	35	9	15/15 (both sexes)	Reeves and Deitch, 1969
		36	35	12	21/21 (both sexes)	Reeves and Deitch, 1969
		36	35	18	13/15 (both sexes)	Reeves and Deitch, 1969

TABLE 4-2 (cont.)

Compound	Species	Atmospheric Concentration (mg/m^3 as Be)	Weekly Exposure Time (hours)	Duration of Exposure (months)	Incidence of Pulmonary Carcinoma	Reference
Beryllium sulfate	rhesus monkeys	35-200	42	8	0/4 (females)	Schepers, 1964
		38.8	15	36+	8/11	Vorwald, 1968
	guinea pigs	35	NR	12	0	Schepers, 1961
		36	35	12	2/20	Schepers, 1971
		3.7-30.4	35	18-24	0/58	Reeves et al., 1972
Beryllium phosphate	rats	32-35	NR	1-12	35-60/170[b]	Schepers, 1961
		227	NR	1-12	7/40[b]	Schepers, 1961
	rhesus monkeys	200	42	8	0/4 (females)	Schepers, 1964
		1100	42	8	1/4 (females)	Schepers, 1964
		8300	42	8	0/4 (females)	Schepers, 1964
Beryllium fluoride	rats	9	NR	6-15	10-20/200	Schepers, 1961
	rhesus monkeys	180	42	8	0/4 (females)	Schepers, 1964
$ZnBeMnSiO_3$	rats	700	NR	9	4-20/220[b]	Schepers, 1961
	rabbits	700	NR	24	0	Schepers, 1961
	guinea pigs	700	NR	22	0	Schepers, 1961
Beryl ore	rats	620	30	17+	18/19	Wagner et al., 1969
	hamsters	620	30	17+	0/48	Wagner et al., 1969
	squirrel monkeys	620	30	17+	0/12	Wagner et al., 1969

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TABLE 4-2 (cont.)

Compound	Species	Atmospheric Concentration (mg/m^3 as Be)	Weekly Exposure Time (hours)	Duration of Exposure (months)	Incidence of Pulmonary Carcinoma	Reference
Betrandite ore	rats	210	30	17+	0/30-60	Wagner et al., 1969
	hamsters	210	30	17+	0/48	Wagner et al., 1969
	squirrel monkeys	210	30	17+	0/12	Wagner et al., 1969

[a]Source: U.S. EPA, 1986A

[b]Number of tumors/number of animals exposed

NR = Not reported

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Incidence of beryllium induced lung cancers ranged from 0-100%. Generally, a latency period of at least 6 months and, preferably, 9 months was required. These studies have been reviewed and evaluated in other recent U.S. EPA (1986a,b) analyses. It is beyond the scope of this document to reproduce these data, particularly since these data are not useful for risk assessment. The most detailed studies of intratracheal injections of beryllium were reported by Spencer et al. (1965, 1968, 1972). In these studies, beryllium oxide fired at different temperatures was injected intratracheally into rats. The results showed that the beryllium oxide fired at the lowest temperature (500°C) had the greatest carcinogenic potency. This beryllium oxide also had the greatest surface area when compared to beryllium oxide fired at 1100 or 1600°C.

Intravenous injection and subperiosteal or intraosseous implantation of beryllium and several of its compounds have been shown to result in osteosarcomas in rabbits (Nash, 1950; Dutra and Largent, 1950; Kawada, 1963; Fodor, 1971; Komitowski, 1969; Tapp, 1969; Yamaguchi and Katsura, 1963; Gardner and Heslington, 1946; Barnes et al., 1950; Sissons, 1950; Cloudman et al., 1949; Hoagland et al., 1950; Janes et al., 1954; Kelly et al., 1961; Higgins et al., 1964: Mazabraud, 1975) and mice (Cloudman et al., 1949). The incidence of osteosarcoma ranged from 0-100% by either route of administration. A latency period of $\geq$9 months seemed to be required.

Beryllium has been studied in mutagenicity assays. Beryllium sulfate was negative in several tests conducted in Salmonella typhimurium both in the presence and absence of S9 (Simmon, 1979a; Rosenkranz and Poirier, 1979; Arlauskas et al., 1985; Simmon et al., 1979). Beryllium was also negative in the pol assay (Rosenkranz and Leifer, 1980) and the WP2 system (Ishizawa, 1979) in Escherichia coli and in Saccharomyces cerevisiae D3 (Simmon et al.,

1979; Simmon, 1979b). Positive reports in microorganisms include the fluctuation test in S. typhimurium strain TA100 (Arlauskas et al., 1985), the rec assay in Bacillus subtilis (Kanematsu et al., 1980; Kada et al., 1980) and the induction of DNA protein adducts in E. coli (Kubinski et al., 1981).

Other studies of the genotoxic potential of beryllium in cultured mammalian cells have been reported. Miyaki et al. (1979) demonstrated the induction of 8-azaguanine-resistant mutants by beryllium chloride in Chinese hamster V79 cells. Hsie et al. (1979a,b) reported the induction of 8-azaguanine-resistant mutants in CHO cells exposed to beryllium sulfate. Larramendy et al. (1981) reported that beryllium sulfate induced chromosomal aberrations in Syrian hamster embryo cells and in human lymphocytes and that beryllium sulfate caused a dose-dependent increase in sister-chromatid exchanges in both Syrian hamster cells and human lymphocytes. These results, however, showed increases in sister-chromatid exchanges that were <2-fold, so that the dose-response relationship suggested by Larramendy et al. (1981) may be somewhat tenuous.

Williams et al. (1982) found that beryllium sulfate did not induce unscheduled DNA synthesis in rat primary hepatocyte cultures. Beryllium sulfate also resulted in no chromosomal effects in human fibroblasts (WI 38 cells) (Paton and Allison, 1972). In vitro exposure of rat liver cells to beryllium resulted in its binding to phosphorylated non-histone proteins (Parker and Stevens, 1979). Perry et al. (1982) found that exposure of cultured rat hepatosomal cells to beryllium reduced the glucocorticoid induction of tyrosine transaminase activity. In a DNA fidelity assay, beryllium increased the misincorporation of nucleotide bases in the daughter strand of DNA synthesized in vitro from polynucleotide templates (Zakour et

al., 1981). Beryllium has also been investigated for its effect on the transcription of calf thymus DNA and phage T_4 DNA by RNA polymerase (from E. coli) under controlled conditions. Beryllium inhibited overall transcription but increased RNA initiation, indicating the interaction of the metal with the DNA template (Niyogi et al., 1981).

4.4. WEIGHT OF EVIDENCE

Beryllium has been shown to be clearly carcinogenic in laboratory animals following inhalation exposure and injection (see Sections 4.2.2. and 4.3.). Epidemiology studies of inhalation exposure (see Section 4.1.2.) are suggestive but have been judged inadequate to demonstrate or refute a carcinogenic potential in humans.

From the available data, IARC (1980) concluded that there is sufficient evidence that beryllium is carcinogenic in animals, but epidemiological evidence that occupational exposure to beryllium may lead to an increased lung cancer risk is only limited. This description is consistent with the IARC Group 2B classification.

Applying the U.S. EPA (1986d) guidelines for carcinogen risk assessment, the evidence from the inhalation animal studies is judged to be sufficient that beryllium is an animal carcinogen. U.S. EPA (1986a) concluded that the human evidence is "inadequate"; therefore, according to the guidelines for evaluating the weight of evidence of carcinogenicity to humans, beryllium is most appropriately classified in Group B2, a probable human carcinogen (U.S. EPA, 1986a). The weight of evidence for beryllium's carcinogenic potential from oral exposure is much less certain given that there are only two studies that provide only suggestive evidence of carcinogenic activity. The data presented in these studies contain inconsistencies that give low confidence to quantitative analysis. The U.S. EPA Carcinogen Assessment Group has stated that ingested beryllium may be capable of inducing a human

carcinogenic response (unlike some other metal for which carcinogenic activity has not been detected) and therefore caution should be exercised until further research is available to define the oral carcinogenic potential of beryllium.

5. REGULATORY STANDARDS AND CRITERIA

Occupational standards for beryllium and compounds have been developed. The ACGIH (1986) TLV-TWA for beryllium and compounds is 0.002 μg/m³ (2 mg/m³,) based primarily on industrial experience. The ACGIH committee is currently reviewing the data regarding beryllium. OSHA (1985) standards for beryllium are 2 μg/m³ as the 8-hour TWA, 5 μg/m³ as the ceiling limit and 25 μg/m³ as the maximum peak above the ceiling concentration to which an individual can be exposed for 30 minutes during an 8-hour shift.

A number of ambient water quality criteria values for beryllium have been derived. U.S. EPA (1980a, 1982), using the statistically insignificant excess of grossly observed tumors at all sites in male rats from the Schroeder and Mitchener (1975a) study and the linearized multistage model, determined that a water concentration of 68 ng/ℓ corresponds to a risk level of 10^{-5}. This value is based on a daily intake of 2 ℓ of water and 6.5 g fish and shellfish for a 70 kg human, and a BCF of 19. This value was also presented in a more recent U.S. EPA (1986b) analysis. A toxicity-based ambient water level of 17.8 μg/ℓ was also calculated from the Schroeder and Mitchener (1975a) study by using the 5 ppm drinking water level as a NOAEL (U.S. EPA, 1980a, 1982). An equivalent dose of 0.538 mg/kg/day was estimated by assuming water consumption of 0.035 ℓ/day and estimating the body weight of exposed rats at 0.325 kg. The water concentration from this NOAEL is equivalent to 0.0377 mg/day for a 70 kg human. An RfD of 5.0×10^{-3} mg/kg/day (0.377 mg/day) based on the 5 ppm NOAEL in the Schroeder and Mitchener, 1975a) study has been derived by the U.S. EPA (1986c).

The U.S. EPA (1986b) derived the following HAs for beryllium:

1-day HA for a 10 kg child, 26 mg/ℓ
1-day HA for a 70 kg adult, 96 mg/ℓ
10-day HA for a 10 kg child, 2.6 mg/ℓ
10-day HA for a 70 kg adult, 9.6 mg/ℓ

An RfD of 0.005 mg/kg/day has also been derived based on the Schroeder and Mitchener (1975a) rat study (U.S. EPA 1986c).

6. RISK ASSESSMENT

6.1 SUBCHRONIC REFERENCE DOSE (RfD_S)

6.1.1. Oral (RfD_{SO}). Beryllium has been shown to be clearly carcinogenic by other routes of exposure, although for the oral route the evidence is less certain. A plausible upper bound estimate of q_1^* has been calculated. Therefore, it is not appropriate to derive an RfD_{SO} value for beryllium or its compounds.

6.1.2. Inhalation (RfD_{SI}). Numerous experiments using laboratory animals have indicated that beryllium is carcinogenic following inhalation exposure; therefore, an RfD_{SI} value will not be derived.

6.2. REFERENCE DOSE (RfD)

6.2.1. Oral (RfD_O). Beryllium has been shown to be clearly carcinogenic by other routes of exposure, and a q_1^* has been calculated for oral exposure. Therefore, it is not appropriate to derive an RfD_O value.

6.2.2. Inhalation (RfD_I). Beryllium has been shown to be carcinogenic in laboratory animals by the inhalation route; therefore, an RfD_I value will not be derived.

6.3. CARCINOGENIC POTENCY (q_1^*)

6.3.1. Oral. Beryllium has been shown to be clearly carcinogenic following inhalation exposure, intratracheal injection, intravenous injection and implantation. To what extent beryllium is carcinogenic by the oral route is largely uncertain, due to the fact that oral absorption data are conflicting. Hyslop et al. (1943), Crowley et al. (1949) and Furchner et al. (1973) indicate that absorption is <1%, while Reeves (1965) estimated that absorption may range from 10-40% of the ingested dose. If beryllium is absorbed following oral exposure, evidence from other routes of exposure indicate that it is also likely to be a carcinogen by the oral route. The

hypothesis is that beryllium's solubility in the gastrointestinal system may be the key to better characterizing the oral carcinogenic risk of beryllium and its salts. This hypothesis, however, has not been fully developed. Because beryllium may pose a carcinogenic risk by the oral route of exposure, a default position has been adopted for calculating a q_1^* despite the clear presence of significant tumor incidences in the two chronic oral studies. The presumption is that the risk would not be any higher than that estimated from a nonsignificant (negative) study and that the value derived is of lower confidence in estimating an upper limit of possible risk. The derived estimate is thought to be only a plausible upper bound due to the hypothesis that the solubility of beryllium salts may be a differentiating factor in beryllium's cancer risk from oral exposure.

In the Schroeder and Mitchener (1975a,b) studies, rats and mice were provided with drinking water containing 5 ppm beryllium sulfate throughout their lifetime. Male rats showed a statistically insignificant increase in the incidence of grossly observed tumors, while female mice showed a small insignificant excess of lymphoma leukemias. In an unpublished study by Morgareidge et al. (1975), rats were exposed to beryllium at concentrations of 5, 50 or 500 ppm in the diet for 2 years. The data from this study were analyzed by U.S. EPA (1986b), which found a significantly higher number of reticulum cell sarcomas in the two lower dose male groups. The relationship between the dose and response was inverse; the most significant response occurred at 5 ppm, and no significant response occurred at 500 ppm. Because of the lack of dose-response, the limitations in design and execution of the study and because these results have never been published, the Morgareidge et al. (1975) study cannot be used to calculate a q_1^*; however, the study does provide evidence that beryllium is carcinogenic following oral exposure.

U.S. EPA (1986b), using Global 82 (Howe and Crump, 1982), calculated a q_1^* from the nonsignificant tumor incidence data in male rats from the Schroeder and Mitchener (1975a) study. The data used to calculate the q_1^* of 4.86 $(mg/kg/day)^{-1}$ is presented in Table 6-1. The water intake value derived to determine the dose level used in the q_1^* calculation was not provided.

6.3.2. Inhalation. Beryllium has been found to be carcinogenic in numerous animal studies. Unfortunately, the animal studies are not well-documented and many were conducted at one dose level. The U.S. EPA (1986a) has used data from 10 studies to calculate potency estimates. These estimates are presented in Table 6-2. Except for the Reeves and Deitch (1969) study, the estimates were derived using the linear nonthreshold dose-response model, which provides conservative risk estimates. The risk estimate from the Reeves and Deitch (1969) study was calculated using a multistage model ADOLLI-83 developed by Crump and Howe (1984). All risk estimates were calculated with and without surface area correction. The surface area correction is used to correct for higher metabolic rates in smaller animals. Because beryllium seems to be sequestered in the lungs and the dose may not be affected by metabolism, it is uncertain whether the surface area correction should be used. Using both methods, q_1^* values of 4.9×10^{-4} to 4.3 $(\mu g/m^3)^{-1}$ were derived. The magnitude of the q_1^* value appears to depend, as a function of its solubility, on the form of beryllium used in the experiment. Beryl ore is the least potent of the four compounds, while beryllium sulfate is the most potent.

The U.S. EPA (1986a) has recommended a q_1^* from human epidemiology data. However, this is an external review draft currently undergoing revision by the Agency. This epidemiological data has been judged to be inadequate for demonstrating or refuting a carcinogenic effect.

TABLE 6-1

Derivation of q_1^* for Beryllium[a]

Reference: Schroeder and Mitchener, 1975a

Species/sex: rat/male

Route/vehicle: oral/drinking water

Length of exposure (le) = 1126 days

Length of experiment (LE) = 1126 days

Lifespan of animal (L) = 1126 days

Body weight = 0.325 kg (measured)[b]

Tumor site and type: gross tumors, all sites

Experimental Exposure	Transformed Dose[c] (mg/kg/day)	Incidence No. Responding/No. Tested
0	0	4/26
5 mg/ℓ	0.455	9/33

Human $q_1^* = 4.86\ (mg/kg/day)^{-1}$

[a]Source: U.S. EPA, 1986b

[b]Body weight average for both sexes estimated from tabular data provided by investigator.

[c]Estimation based on the assumption that rats consumed 0.35 ℓ of water/day.

TABLE 6-2

Beryllium Dose-Response From 10 Inhalation Studies on Animals and the Corresponding Potency (Slope) Estimations[a]

Species	Beryllium Compound	Mean Beryllium Concentration Exposure Pattern	Standardized Experimental Concentration[b] (μg/m³)	Pulmonary Tumor Incidence Rate	Surface Area Correction	Human Equivalent Concentration (μg Be/m³)	Maximum Likelihood Estimate Slope[c,d] $(\mu g/m^3)^{-1}$	Reference
Rats	beryllium sulfate	33 μg/Be/m³, 35 hours/week for 13 months	5.0	4/8	+	1.9	3.7×10^{-1}	Vorwald, 1953
					-	11.2	6.3×10^{-2}	
		33.5 μg/Be/m³, 35 hours/week for 7.5 months	2.9	58/136	+	1.1	5.0×10^{-1}	Schepers' et al., 1957
					-	6.5	8.6×10^{-2}	
	beryllium phosphate	217 μg/Be/m³, 35 hours/week for 6.5 months	17.1	7/40	+	6.5	3.0×10^{-1}	Schepers, 1961
					-	39.6	5.0×10^{-2}	
	beryllium fluoride	9 μg/Be/m³, 35 hours/week for 10.5 months	1.1	11/200	+	0.42	1.4×10^{-1}	Schepers, 1961
					-	2.5	2.4×10^{-2}	
	beryllium sulfate	2.8 μg/Be/m³, 35 hours/week for 18 months	0.58	13/21	+	0.22	4.3×10^{0}	Vorwald et al., 1966
					-	1.30	7.4×10^{-1}	
		35.7 μg/Be/m³, 35 hours/week for 18 months	7.4	13/15	+	2.8	7.1×10^{-1}	Reeves and Deitch, 1969
					-	16.6	1.2×10^{-1}	
	beryl ore	620 μg/Be/m³, intermittently for 17 months	585.6	9/19	+	223.4	2.9×10^{-3}	Wagner et al., 1969
					-	1306.4	4.9×10^{-4}	
	beryllium sulfate	35.7 μg/Be/m³, 35 hours/week for HOW LONG?	NR	NR	+	NR	8.1×10^{-1}	Reeves and Deitch, 1969
					-		1.4×10^{-1}	

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TABLE 6-2 (cont.)

Species	Beryllium Compound	Mean Beryllium Concentration Exposure Pattern	Standardized Experimental Concentration[b] (μg/m³)	Pulmonary Tumor Incidence Rate	Surface Area Correction	Human Equivalent Concentration (μg Be/m³)	Maximum Likelihood Estimate Slope[c,d] $(\mu g/m^3)^{-1}$	Reference
Guinea pigs	beryllium sulfate	36 μg/Be/m³, 35 hours/week for 12 months	5.1	2/20	+	1.7	6.5×10^{-2}	Schepers, 1971
					-	8.8	1.2×10^{-2}	
Rhesus monkeys[e]	beryllium sulfate	38.8 μg/Be/m³, 15 hours/week for 3 years	0.69	8/11	+	0.36	3.6×10^{0}	Vorwald, 1968
					-	1.04	1.2×10^{0}	

[a]Source: U.S. EPA, 1986a

[b]Standardized experimental dose is calculated by d x (h/168) x le/Le, where d is the mean experimental concentration, h is the number of hours exposed/week (168 hours), le is the number of months exposed and Le is the length of the experiment.

[c]Estimated by assuming that the control response is zero.

[d]Calculated using linear nonthreshold dose-response model for all studies except Reeves and Deitch (1969) for which a multistage model, ADOLLI-83, developed by Crump and Howe (1984) was used.

[e]A lifespan of 15 years is assumed.

NR = Not reported

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The usual approach in risk assessment is to accept the most conservative estimate of carcinogenic risk, which in this case would be 4.3 $(\mu g/m^3)^{-1}$, calculated from the rat study by Vorwald et al. (1966). The U.S. EPA (1986a) suggested that the use of this animal potency estimate would overestimate the human risk and is not consistent with human experience in the beryllium industry. Therefore, U.S. EPA (1986a) recommends 2.4×10^{-3} $(\mu g/m^3)^{-1}$ as the estimate of risk associated with 1 $\mu g/m^3$ of beryllium in air. This estimate is the geometric mean of eight q_1^*s calculated on the basis of human data under various assumptions (Table 6-3). The estimate of 2.4×10^{-3} $(\mu g/m^3)^{-1}$ could be considered to be an upper-bound estimate of the cancer risk because low dose linearity is assumed in the extrapolation and the 95% upper confidence limits of the relative risks are used in the calculations. Transforming to units of $(mg/kg/day)^{-1}$, the unit risk of 2.4×10^{-3} $(\mu g/m^3)^{-1}$ is equivalent to 8.4 $(mg/kg/day)^{-1}$.

Because the carcinogenic potency seems to be related to beryllium's solubility, the U.S. EPA (1986a) cautions that beryllium species identification is likely to be a very important aspect of properly characterizing the possible oral or inhalation exposure risk to humans. U.S. EPA (1986a) is an external draft document that is currently undergoing revision, therefore a final recommended unit risk (q_1^* value) will have to await the finalization of this document.

TABLE 6-3

Upper-Bound Cancer Potency Estimates Calculated Under Various Assumptions[a]

Beryllium Concentration in Workplace ($\mu g/m^3$)	f/L	Effective Dose[b] ($\mu g/m^3$)	95% Upper-Bound Estimate of Relative Risk	Cancer Potency[c] $(\mu g/m^3)^{-1}$
100	1	21.92	1.98	1.61×10^{-3}
			2.09	1.79×10^{-3}
	0.25	5.48	1.98	6.44×10^{-3}
			2.09	7.16×10^{-3}
1000	1	219.18	1.98	1.61×10^{-4}
			2.09	1.79×10^{-4}
	0.25	54.79	1.98	6.44×10^{-4}
			2.09	7.16×10^{-4}

[a]Source: U.S. EPA, 1986a

[b]Effective dose is calculated by multiplying the beryllium concentration in the workplace by the factor (8/24)x(240/365)x(f/L) (f = years exposed; L = years at risk).

[c]For a given effective dose (d) and a relative risk (R), the carcinogenic potency is calculated by the formula B = (R-1) x 0.036/d, where 0.036 is the estimated lung cancer mortality rate in the United States population.

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APPENDIX

Summary Table for Beryllium

Route	Species	Experimental Exposure/Dose	Effect	q_1^* or Unit Risk	Reference
Inhalation	animal	experimental concentrations 0.69-585.6 µg/m³. Standardize experimental calculated by d x (h/168) x 1e/Le.	pulmonary tumors	range: $q_1^* = 4.9 \times 10^{-4}$ to 4.3 $(\mu g/m^3)^{-1}$	U.S. EPA, 1986a
Oral	rat (male)	5 mg/L drinking water lifetime, 0.455 mg/kg/day	nonsignificant excess in gross tumors	$q_1^* = 4.86$ $(mg/kg/day)^{-1}$	Schroeder and Mitchener, 1975a; U.S. EPA, 1986b

†Estimated from 10 animal studies to calculate a range of potency estimates